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CONJUGATES OF DERMATAN SULFATE WITH BIOLOGICALLY ACTIVE AMINES

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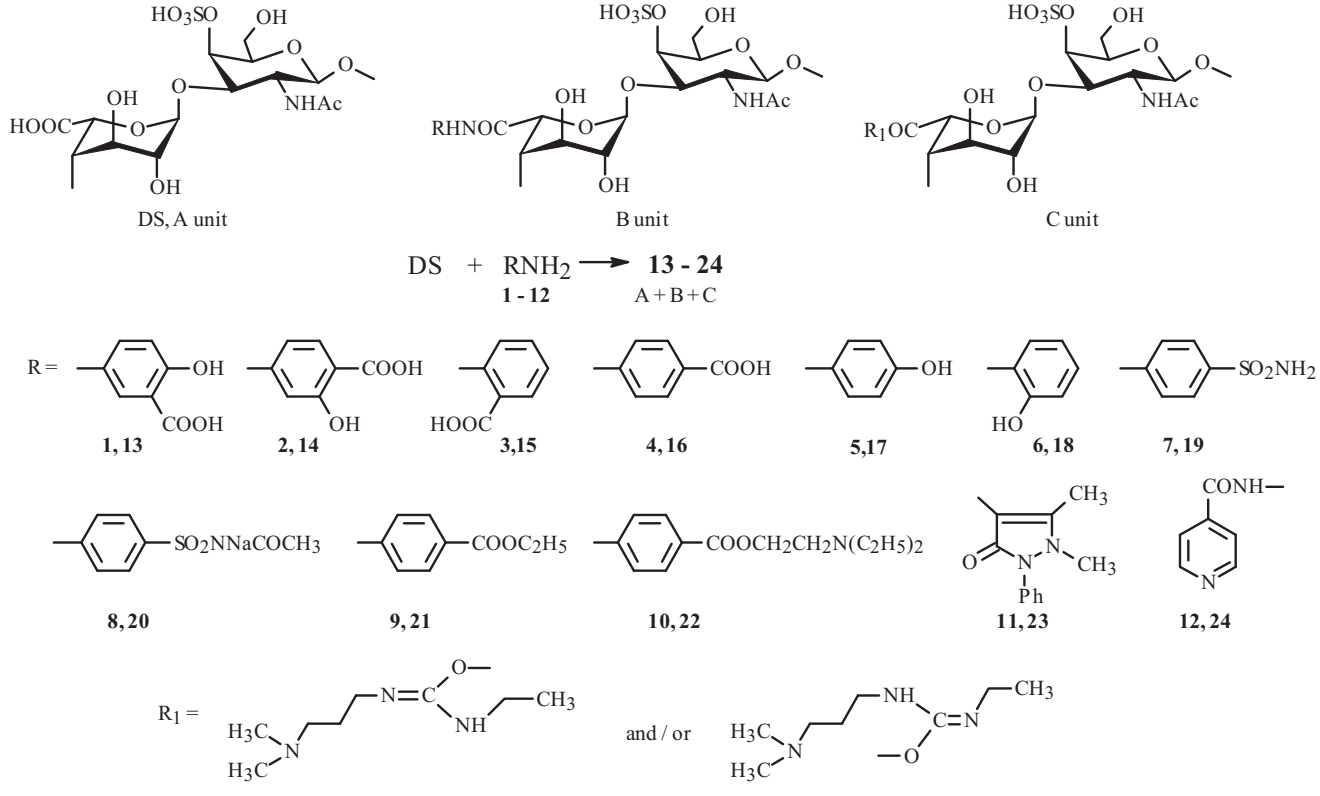
Dermatan sulfate (chondroitin sulfate B, DS) is a representative of the glycosaminoglycan class. It is a linear heteropolysaccharide, the disaccharide unit of which consists of L-iduronic acid and *N*-acetyl-4-sulfo-D-galactosamine[1] [1]. DS occurs in practically all types of connective matrix and fulfills important biological functions *in vivo*, participating in the biosynthesis of collagen fibrils; cytokinesis, proliferation, differentiation, and migration of cells; morphogenesis of tissues; and development of reparative processes [2, 3]. At present DS has limited application in medicine. However, its high therapeutic potential is attractive for developing new drugs with antiparasitic, antiviral, antitumor, and reparative and regenerative properties [3, 4].

We incorporated into the structure of DS (isolated from pig skin [5]) several amines with anti-inflammatory, antimicrobial, anesthetic, and nutritional properties in order to expand the spectrum of its biological and pharmacological activity [6].



Scheme 1

[1]Depending on the source, DS can contain D-glucuronic acid and L-iduronic acid sulfated at the C-2 hydroxyl. DS from pig skin usually contains up to 20% D-glucuronic acid units [1].

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TABLE 1. Properties of DS Conjugates **13**–**24**

Amine (conjugate)	UV spectrum (H_2O, λ_{max}, nm)	PMR spectrum* (300 MHz, D_2O, δ, ppm)		Content of units, mol%		
		MeCON**	H_{Ar}	A	B	C
5-Aminosalicylic acid (**13**)	313	1.42, 2.11	7.0, 7.7, 8.1	67	30	3
4-Aminosalicylic acid (**14**)	266 and 304	1.42, 2.11	7.1, 7.3, 7.9	62	28	10
Anthranilic acid (**15**)	300	1.49, 2.16	7.3, 7.7, 8.1, 8.7	29	71	0
p-Aminobenzoic acid (**16**)	289	1.46, 2.11	7.8, 8.0	62	33	5
p-Aminophenol (**17**)	247	1.44, 1.74, 2.10	7.0, 7.5	25	65	10
o-Aminophenol (**18**)	282	1.52, 1.86, 2.10	7.1, 7.3, 7.9	25	52	23
p-Aminobenzenesulfamide (streptocide) (**19**)	259	1.72, 2.07	7.6, 7.9	30	26	44
p-Aminobenzenesulfacetamide sodium (sulfacil sodium) (**20**)	264	2.04, 2.17	7.8, 7.9	30	20	50
Ethyl *p*-aminobenzoate (anesthesin) (**21**)	271	1.43, 1.71, 2.07	7.8, 8,1	15	40	45
β-Diethylaminoethyl *p*-aminobenzoate (novocaine) (**22**)	273	1.70, 2.10	7.9, 8.0	35	33	32
1-Phenyl-2,3-dimethyl-4-aminopyrazolone-5 (4-aminoantipyrine) (**23**)	261	1.89, 2.11	7.5, 7.7	48	52	0
Isonicotinic acid hydrazide (isoniazid) (**24**)	263	2.11	8.0, 8.9	55	42	3

*A characteristic resonance with δ 2.0 ppm (s, CH_3CO) was observed in the PMR spectrum of **20**; with δ 1.5 (t, J = 7.0 Hz, $C\underline{H}_3CH_2O$) and 4.5 ppm (m, $CH_3C\underline{H}_2O$), of **21**; with δ 1.4 [t, J = 7.0 Hz, $N(CH_2C\underline{H}_3)_2$], of **22**; and with δ 1.9 and 2.4 (s, $C{=}CCH_3$) and 3.4 ppm (s, CH_3N); of **23**. A characteristic resonance for methyl protons of $(CH_3)_2N$ was observed at δ 2.8–3.0 ppm for conjugates containing unit C. **Methyl resonance in the range δ 2.07–2.17 ppm was the principal one for MeCON in DS. Additional resonances of this group appeared at stronger field (1.42–1.89 ppm) because of the shielding effect of the magnetically anisotropic phenyl ring [7].

Reaction of DS (75 mg, 0.15 mmol) in H_2O (20 mL) with amines **1**–**12** and CDI (1:1:1.5 ratio) at pH 4.7–4.8 for 2 h afforded the corresponding conjugates **13**–**24** (60–70 mg) (Scheme 1). Table 1 presents the yields (contents of units A, B, and C in mol%) and UV and PMR spectra. The content of amide units B that was found from the intensity ratio per aromatic proton resonance of the corresponding amine (7.0–8.9 ppm) and CH_3CON methyl protons (δ 1.42–2.17 ppm) was 20–71% for conjugates **13**–**24** (Table 1). The content of CDI addition products at the DS *O*-isoureide carboxyl (units C) that was calculated from the intensity ratio per $(CH_3)_2N$ methyl proton resonances (2.8–3.0 ppm) and CH_3CON varied over wide ranges and reached 23, 44, 50, 45, and 32 in conjugates **18** (*o*-aminophenol), **19** (streptocide), **20** (sulfacil sodium), **21** (anesthesin), and **22** (novocaine), respectively (Table 1).

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